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Risk Factors and Overcoming Strategies of Surgical Site Infection After Hepatectomy for Colorectal Liver Metastases

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Abstract. *Background/Aim: The aim of this study was to investigate the risk factors of surgical site infection (SSI) in patients who underwent liver resection for colorectal liver metastases (CRLM). Patients and Methods: A total of 151 patients who underwent liver resection for CRLM were included in this study. We investigated the relationship between the patient characteristics and perioperative factors and the incidence of SSI. Results: Nineteen (13%) of these patients developed SSI. Multivariate analysis revealed that modified Glasgow Prognostic Score (mGPS) (1 or 2, odds ratio 3.86, p=0.03) and presence of an enterostomy (yes, odds ratio 3.93, p=0.04) were significant and independent risk factors for SSI. Conclusion: A higher mGPS and an enterostomy were risk factors for SSI in patients who underwent a liver resection for CRLM.*

Colorectal cancer is one of the most common cancers worldwide, and has a yearly increase in incidence (1). The liver is the most common site of metastases with approximately half of patients developing liver metastases (2). Surgical resection is the only current treatment that can provide possible prolonged survival for patients with colorectal liver metastases (CRLM) (3), with a 5-year survival rate reaching 33% to 50% (4).

Although liver resection has become safer due to improved surgical techniques and perioperative management, morbidity rates still remain high. Bile leakage and surgical site infection (SSI) are common causes of major morbidities after liver resection (5, 6), and SSI is the most frequent complication with an incidence ranging from 13% to 15% (7, 8).

Moreover, the negative impact of postoperative complications on long-term outcomes has been reported in patients undergoing liver resection for CRLM (9-14). However, the mechanisms by which postoperative complications affect long-term survival remain unknown. Further, delayed initiation of chemotherapy after surgery due to postoperative complications may be associated with poor survival and acceleration of the inflammatory response, creating a favorable environment for faster progression of microscopic cancer and immunosuppression (15, 16). Therefore, efforts to improve perioperative management to reduce postoperative complications, including SSI, are necessary to improve cancer-specific outcomes for patients with CRLM.

The purpose of this study was to investigate risk factors of SSI in patients who underwent liver resection for CRLM and to establish methods to reduce the prevalence of SSI which may lead to improved prognosis.

Patients and Methods

Patients. Between May 2007 and March 2020, 151 consecutive patients with CRLM who underwent an initial liver resection, excluding staged hepatectomies, at the Department of Surgery, Jikei University Hospital, Tokyo, Japan were included in the study. A database of patients was prospectively recorded and analyzed retrospectively. This study was approved by the Ethics Committee of the Jikei University School of Medicine (27-177).

Perioperative management. All patients with no unresectable extrahepatic tumors underwent liver resection regardless of the size, number, or location of the liver metastases, as long as curative resection would leave sufficient remnant liver. Generally, parenchymal-sparing hepatectomy was performed and the extent of hepatic resection was determined based on the retention rate of indocyanine green at 15 min (ICGR15) (17). Percutaneous transhepatic portal embolization was performed for patients with an estimated residual hepatic volume of less than 30%. Anatomical

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Key Words: Risk factor, surgical site infection, colorectal liver metastases, liver resection.

Table I. *Patient characteristics*.

Variables	Total (n=151)	Surgical site infections		*p*-Value
		Yes (n=19)	No (n=132)	
Age, yeas	66 (58-73)	72 (58-76)	66 (58-72)	0.38
Gender, male	107 (71%)	15 (79%)	92 (70%)	0.41
Body mass index, kg/m^2	22.3 (20.1-24.2)	22.5 (19.1-24.1)	22.3 (20.4-24.2)	0.51
Diabetes	27 (18%)	3 (16%)	24 (18%)	0.80
Timing of tumor, synchronous	97 (64%)	13 (68%)	84 (64%)	0.68
Neoadjuvant chemotherapy	56 (37%)	8 (42%)	48 (36%)	0.63
mGPS, 1 or 2	40 (26%)	11 (58%)	29 (22%)	<0.01
CPR/Alb ratio	0.03 (0.01-0.11)	0.07 (0.03-0.18)	0.03 (0.01-0.09)	0.05
Tumor size, mm	26 (17-44)	43 (26-58)	25 (16-39)	<0.01
Tumor number	2 (1-3)	2 (1-4)	2 (1-3)	0.30
Tumor location, center	55 (36%)	10 (53%)	45 (34%)	0.12
Enterostomy	27 (36%)	10 (53%)	45 (34%)	0.02
Simultaneous resection	42 (28%)	7 (37%)	35 (27%)	0.35
Laparoscopic hepatectomy	30 (20%)	1 (5%)	29 (22%)	0.09
Anatomical hepatectomy	79 (52%)	15 (79%)	64 (48%)	0.01
Operation time, min	368 (275-480)	488 (353-545)	361 (257-461)	0.03
Intraoperative blood loss, ml	450 (150-1,050)	1,046 (398-1,651)	420 (120-990)	<0.01
RBC transfusion	34 (23%)	11 (58%)	23 (17%)	<0.01
Postoperative biloma	24 (16%)	4 (21%)	11 (8%)	0.08
Length of postoperative stay, days	12 (9-16)	19 (13-30)	11 (9-14)	<0.01

Alb: Albumin; CRP: C-reactive protein; mGPS: modified Glasgow Prognostic Score; RBC: red blood cells.

resection included extended lobectomy, lobectomy, segmentectomy or sub-segmentectomy and non-anatomical resection limited partial resection.

For tumor staging, contrast-enhanced computed tomography and gadoxetic acid-enhanced magnetic resonance imaging were performed routinely. The center tumor was defined as the tumor close to the main or second branches of Glisson's tree, within 1 cm. Neoadjuvant chemotherapy was given when liver metastases were unresectable or borderline.

Prophylactic antibiotics were given to all patients just before incision of the skin and every 3 hours during the operation. Parenchymal transection was performed under intraoperative ultrasonographic guidance using a Cavitron Ultrasonic Surgical Aspirator (CUSA™, Valletlab Inc., Boulder, CO, USA), with or without Pringle's maneuver. After the resection, the fascia was closed with interrupted absorbable sutures and the wound was closed with a skin stapler.

Definition of SSI. SSI was defined as a condition where purulent discharge was observed with or without microbiological evidence in the incision or in an organ or space. Organ or space infection was determined by radiologic evidence of fluid collection, necessitating antibiotic therapy or drainage. Biloma was defined as a bile discharge from the abdominal drainage tube or fluid collection.

Assessment of systemic inflammatory response. A chemistry profile was preoperatively measured in patients. The systemic inflammatory response was assessed using the Japanese Modified Glasgow Prognostic Score (mGPS) and C-reactive protein (CRP)/albumin (Alb) ratio. The mGPS was calculated on the basis of preoperative data as follows: patients with normal Alb (≥3.5 mg/dl) and normal CRP (≤0.5 mg/dl) levels were assigned an mGPS of 0, low Alb (<3.5 mg/dl) or elevated CRP (>0.5 mg/dl) levels as an mGPS of 1, and both low Alb (<3.5 mg/dl) and elevated CRP (>0.5 mg/dl) levels as an mGPS of 2 (18, 19). The CRP/Alb ratio was calculated by dividing the levels of serum CRP (mg/l) by those of serum Alb (g/l).

Statistical analysis. The data are expressed as the median (interquartile range). We investigated the relation between patient characteristics and perioperative factors and the incidence of SSI using the Mann-Whitney *U* and Chi-square tests. The factors included age, gender, body mass index, diabetes (yes or no), timing of tumor (synchronous or metachronous), neoadjuvant chemotherapy (yes or no), mGPS (0 or 1, 2), CRP/Alb ratio, tumor size, tumor number, tumor location (center or peripheral), enterostomy (yes or no), simultaneous resection (yes or no), laparoscopic hepatectomy (yes or no), anatomical hepatectomy (yes or no), operative time, intraoperative blood loss, intraoperative red blood cells (RBC) transfusion (yes or no), postoperative biloma (yes or no), and length of postoperative stay. Predictive factors for SSI were further analyzed using univariate and multivariate logistic regression models. Based on the receiver operating characteristic curve coordinates, the most optimal cut-off points for tumor size, operative time, and intraoperative blood loss were determined as 40 mm, 450 min, and 950 ml, respectively, and 0.04 was used as the cut-off point for the CRP/Alb ratio according to our previous study (20). Next, we compared an mGPS of 0 and 1 or 2 by univariate analysis. The variables consisted of the above factors, including levels of serum carcinoembryonic antigen (CEA).

All *p*-values were considered statistically significant when the associated probability was <0.05.

Table II. *Univariate and multivariate analyses for surgical site infections.*

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*p*-Value	Odds ratio (95%CI)	*p*-Value
Age, yeas	0.98 (0.94-1.03)	0.47		
Gender, male	1.63 (0.51-5.2)	0.41		
Body mass index, kg/m^2	1.05 (0.90-1.24)	0.52		
Diabetes, yes	0.84 (0.23-3.13)	0.80		
Timing of tumor, synchronous	1.24 (0.44-3.47)	0.68		
Neoadjuvant chemotherapy, yes	1.27 (0.48-3.38)	0.63		
mGPS, 1 or 2	4.88 (1.80-13.27)	<0.01	3.86 (1.11-13.41)	0.03
CPR/Alb ratio, ≥0.04	2.76 (0.99-7.72)	0.05		
Tumor size, ≥40 mm	3.33 (1.25-8.91)	0.02	1.33 (0.37-4.86)	0.66
Tumor number	0.87 (0.74-1.03)	0.11		
Tumor location, center	2.15 (0.81-5.67)	0.12		
Enterostomy, yes	3.27 (1.15-9.30)	0.03	3.93 (1.08-14.30)	0.04
Simultaneous resection, yes	1.62 (0.59-4.44)	0.35		
Open hepatectomy, yes	5.07 (0.65-39.59)	0.12		
Anatomical hepatectomy, yes	3.98 (1.26-12.64)	0.02	1.47 (0.33-6.61)	0.62
Operation time, ≥450 min	4.75 (1.73-13.03)	<0.01	2.26 (0.67-7.66)	0.19
Intraperative blood loss, ≥950 ml	4.94 (1.80-13.57)	<0.01	2.69 (0.66-11.00)	0.17
RBC transfusion, yes	6.52 (2.36-18.00)	<0.01	2.40 (0.69-8.41)	0.17
Postoperative biloma, yes	2.93 (0.83-10.38)	0.08		

Alb: Albumin; CI: confidence interval; CRP: C-reactive protein; mGPS: modified Glasgow Prognostic Score; RBC: red blood cells.

Results

Comparison of patients with and without SSI. Out of 151 total patients, 19 (12.5%) developed SSI, 17 (11.3%) were diagnosed with an incisional SSI, and 2 (1.3%) were diagnosed with an organ/space SSI. Table I lists the association between patient characteristics and perioperative factors and the incidence of SSI. Patients who developed SSI had an increased incidence of an mGPS of 1 or 2 (58% *vs*. 22%, $p<0.01$), larger tumors (43 *vs*. 25 mm, $p<0.01$), increased presence of enterostomy (53% *vs*. 34%, $p=0.02$), increased incidence of undergoing anatomical hepatectomy (79% *vs*. 48%, $p=0.01$), longer operative times (488 *vs*. 361 min, $p=0.03$), more intraoperative blood loss (1,046 *vs*. 420 ml, $p<0.01$), increased incidence of RBC transfusion (58 *vs*. 17%, $p<0.01$), and longer length of postoperative stay (19 *vs*. 11 days, $p<0.01$) than those without SSI.

Correlation of variables with SSI by univariate and multivariate logistic regression models. Table II lists the association between SSI and variables using logistic regression analysis. In the univariate analysis, significant predictors of SSI consisted of an mGPS of 1 or 2 ($p<0.01$), tumor size ≥40 mm ($p=0.02$), enterostomy ($p=0.03$), anatomical hepatectomy ($p=0.02$), operative time ≥450 min ($p<0.01$), intraoperative blood loss ≥950 ml ($p<0.01$), and RBC transfusion ($p<0.01$). Multivariate analysis revealed that an mGPS of 1 or 2 (odds ratio 3.86, 95% confidence interval=1.11-13.41, $p=0.03$) and enterostomy (odds ratio 3.93, 95% confidence interval 1.08-14.30, $p=0.04$) were significant and independent risk factors for SSI.

Association between patient characteristics and mGPS. Table III lists the association between patient characteristics and mGPS. The univariate analysis revealed that patients with an mGPS of 1 or 2 were significantly older (72 *vs*. 65 years, $p<0.01$), underwent a lower number of neoadjuvant chemotherapies (23 *vs*. 42%, $p=0.03$), had higher serum CEA levels (27 *vs*. 8 ng/ml, $p<0.01$), had larger tumor size (44 *vs*. 23 mm, $p<0.01$), had more central tumors (53% *vs*. 31%, $p=0.01$), underwent more procedures of simultaneous resection (45% *vs*. 22%, $p<0.01$), underwent a lower number of laparoscopic hepatectomies (5% *vs*. 25%, $p<0.01$), underwent more RBC transfusions (38% *vs*. 17%, $p<0.01$), and had a longer length of postoperative stay (14 *vs*. 11 days, $p<0.01$) than those with an mGPS of 0.

Association of SSI and enterostomy according to operative procedure. Figure 1 shows that patients with an enterostomy who underwent pure laparoscopic hepatectomy had a significantly decreased incidence of SSI than others ($p=0.01$).

Discussion

Several investigators have reported on the factors associated with SSI in patients who underwent hepatectomies. The

Table III. *Patient characteristics in relation to mGPS.*

Variables	mGPS		*p*-Value
	0 (n=111)	1 or 2 (n=40)	
Age, yeas	65 (57-72)	72 (65-77)	<0.01
Gender, male	76 (68%)	31 (78%)	0.28
Body mass index, kg/m^2	22.5 (19.1-24.1)	22.3 (20.4-24.2)	0.51
Diabetes	16 (14%)	11 (28%)	0.06
Timing of tumor, synchronous	68 (61%)	29 (73%)	0.20
Neoadjuvant chemotherapy	47 (42%)	9 (23%)	0.03
Serum CEA, ng/ml	8 (4-29)	27 (8-168)	<0.01
Tumor size, mm	23 (16-34)	44 (25-72)	<0.01
Tumor number	2 (1-3)	1 (1-2)	0.19
Tumor location, center	34 (31%)	21 (53%)	0.01
Enterostomy	18 (16%)	9 (23%)	0.37
Simultaneous resection	24 (22%)	18 (45%)	<0.01
Laparoscopic hepatectomy	28 (25%)	2 (5%)	<0.01
Anatomical hepatectomy	55 (50%)	24 (60%)	0.26
Operation time, min	359 (270-470)	395 (294-492)	0.26
Intraoperative blood loss, ml	415 (125-1,038)	610 (265-1,215)	0.08
RBC transfusion	19 (17%)	15 (38%)	<0.01
Postoperative biloma	8 (7%)	7 (18%)	0.06
Length of postoperative stay, days	11 (9-15)	14 (11-21)	<0.01

CEA: Carcinoembryonic antigen; mGPS: modified Glasgow Prognostic Score; RBC: red blood cells.

reported risk factors were: increased operative duration, smoking, dialysis, decreased serum sodium, decreased serum Alb, open wound (21), bowel injury, increased blood loss, increased age (22), silk sutures, and bile leakage (23). The current study revealed that a higher mGPS and the presence of an enterostomy were statistically significant risk factors for SSI in patients who underwent a hepatectomy for CRLM. In fact, to our knowledge, this is the first report suggesting that a higher mGPS and the presence of an enterostomy were risk factors for SSI in patients who underwent a hepatectomy for CRLM.

Inflammation-based prognostic scoring systems have proven to be valuable prognostic factors in cancer patients. Preoperative systemic inflammation, represented by mGPS, neutrophil-to-lymphocyte ratio, and the CRP/Alb ratio have been reported to predict cancer-specific survival, including CRLM (20, 24, 25). Most studies on an inflammation-based prognostic scoring system primarily focused on the oncologic prognosis and rarely reported on the predictors of postoperative complications (26). Based on the result that a higher mGPS was a risk factor for SSI in patients who underwent hepatectomy for CRLM, we hypothesized that improving the preoperative mGPS could lead to a reduction in postoperative SSI. We found that patients with an mGPS of 1 or 2 were significantly older, underwent a lower number of neoadjuvant chemotherapies, had higher serum CEA levels, and had larger tumor sizes and more central tumors than those with an mGPS of 0. This indicates that advanced CRLM without neoadjuvant chemotherapy could be associated with a higher mGPS. The role of neoadjuvant chemotherapy in patients with resectable CRLM is ambiguous (27, 28). However, neoadjuvant chemotherapy combined with nutritional therapy for advanced CRLM with large and central tumors and high CEA levels may be an effective strategy to reduce SSI by improving the mGPS (Figure 2).

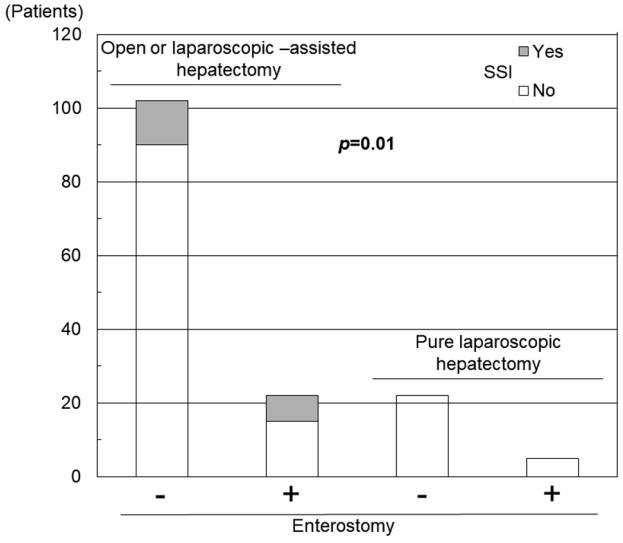

Figure 1. *Incidence of surgical site infections (SSI) in patients with or without an enterostomy according to operative procedure.*

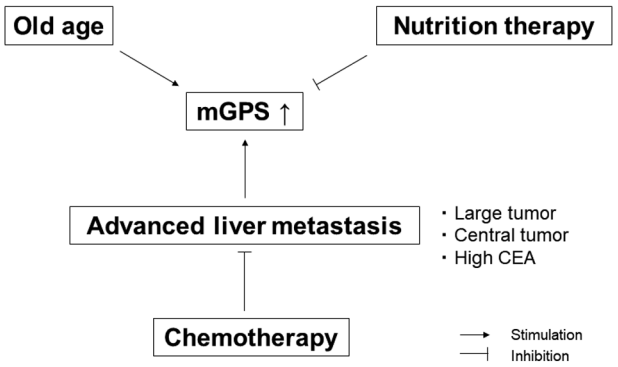

Figure 2. *Strategies to improve the modified Glasgow Prognostic Score (mGPS). Neoadjuvant chemotherapy combined with nutritional therapy for advanced liver metastases could be an effective strategy to improve the mGPS.*

The present study showed that the presence of an enterostomy was a significant risk factor for SSI in patients who underwent a hepatectomy for CRLM. Ricciardi *et al*. reported that in colorectal surgery, the construction of an enterostomy was associated with a higher risk of SSI and this association was attenuated with laparoscopic surgery (29). Laparoscopic hepatectomies have been performed in a limited number of centers, but technological innovations, improvement in surgical techniques, and experienced surgeon have led to a rapid progression of laparoscopic hepatectomy (30, 31). Furthermore, a laparoscopic hepatectomy was shown to decrease postoperative complications, including SSI (31, 32). Our study showed that patients with an enterostomy who underwent a pure laparoscopic hepatectomy had a significantly decreased incidence of SSI than others. Further, Jin *et al*. reported that laparoscopic hepatectomy for patients with CRLM and an enterostomy were feasible (33), suggesting that a pure laparoscopic hepatectomy could be an effective strategy to reduce SSI for patients with an enterostomy.

Unfortunately, the limitation of this study is that it is a retrospective study, and a prospective randomized study is necessary for validating our strategies to reduce SSI.

In conclusion, a higher mGPS and the presence of an enterostomy were independent risk factors for SSI in patients who underwent a hepatectomy for CRLM. We believe that neoadjuvant chemotherapy combined with nutritional therapy for patients with an mGPS of 1 or 2 and a pure laparoscopic liver resection for patients who have an enterostomy can decrease the incidence of SSI after liver resection for CRLM, resulting in a better prognosis.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Kenei Furukawa: Design of the study, collection and analysis of data and drafting of the article. Shinji Onda, Tomohiko Taniai, Ryoga Hamura, Mitsuru Yanagaki, Masashi Tsunematsu, Koichiro Haruki, Jungo Yasuda, Taro Sakamoto, Takeshi Gocho: Collection of data. Toru Ikegami: Revision of the article and final approval of the article.

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